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(54) Parenteral drug delivery composition

(57) The composition comprises an aqueous solution of a drug and a glucose polymer mixture which includes at least 50% by weight of glucose polymers of D.P greater than 12. The composition is introduced into the peritoneal cavity. The drug is e.g. erythropoeitin or a cephalosporin.

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PARENTERAL DELIVERY OF DRUGS AND COMPOSITIONS FOR USE THEREIN

The present invention relates to drug delivery, i.e. the administration of drugs to patients.

Drugs are administered to patients enterally (orally, rectally or sublingually) or parenterally (intravenously, subcutaneously, or by inhalation). The most convenient method of administration is by mouth but not all drugs can effectively be taken orally. Some drugs are unstable in the conditions prevailing in the gastro-intestinal tract. Others, though stable in these conditions, are not easily absorbed through the walls of the gut, because the drug molecules are too large and/or because they are electrically charged in such a way as to inhibit their passage through the intestinal walls. In many cases, such drugs can be best administered to the patient by intravenous injection.

There are also drugs which can be administered by mouth without difficulty (in that they are stable in the gastro-intestinal tract and pass readily from the gut into the blood), but which are unstable in the bloodstream and are so rapidly degraded as to have only a short half-life therein; it is therefore difficult to maintain a therapeutically effective level of the drug in the blood. These drugs can be administered by frequent intravenous injection or in some cases by subcutaneous injection, the latter technique involving the formation in muscular tissue of a depot of the drug from which the drug is gradually released to find its way into the bloodstream.

This invention is concerned with a new method of parenteral administration of drugs and with compositions for use therein. The invention is particularly concerned with problems arising in

connection with a group of relatively new drugs which is at present of great interest. Many bodily functions appear to be controlled by substances such as peptides and proteins. Modern techniques of genetic engineering have made it possible to produce compounds similar to (in some cases substantially identical with) human peptides or proteins. It is hoped that such drugs, which for convenience will be referred to herein as "peptide drugs" will, like body peptides, be more selective in action than conventional drugs and will therefore be less likely to give rise to unwanted side-effects.

Unfortunately, these peptide drugs are relatively unstable in the gastro-intestinal tract. Also, because they are large and because they are electrically charged, they do not easily pass through the walls thereof into the bloodstream. They are therefore usually administered parenterally. However, they are rapidly degraded in the blood, so that they have a short duration of action, with the result that frequent injections are necessary to maintain a sufficient concentration in the blood. This presents considerable inconvenience, especially when the drug is to be used for treatment of a chronic condition and may therefore have to be administered throughout the lifetime of the patient. Attempts have been made to administer peptide drugs through the nasal membrane but have met with only limited success.

It is an object of this invention to provide an improved method of parenteral delivery of peptide drugs and to provide

compositions for use in such a method.

Accordingly the invention provides a method of parenterally administering a drug to a patient comprising introducing into the peritoneal cavity of the patient an aqueous solution containing said drug and also containing a glucose polymer mixture which comprises at least 50% by weight of glucose polymers of D.P. greater than 12. (D.P. is an abbreviation for "Degree of Polymerisation".)

It is known that introduction of certain aqueous solutions into the peritoneal cavity can be useful in the treatment of patients suffering from renal failure. Such treatment is known as peritoneal dialysis. The solutions contain electrolytes similar to those present in plasma; they also contain an osmotic agent, normally dextrose, which is present in a concentration sufficient to create a desired degree of osmotic pressure across the peritoneal membrane. Under the influence of this osmotic pressure, an exchange takes place across the peritoneal membrane and results in withdrawal from the bloodstream of waste products, such as urea and creatinine, which have accumulated in the blood due to the lack of normal kidney function. While this exchange is taking place, there is also a net transfer of dextrose from the solution to the blood across the peritoneal membrane, which causes the osmolality of the solution to fall. Because of this, the initial osmolality of the solution must be made fairly high (by using a sufficiently high concentration of dextrose) in order that the solution continues to effect dialysis for a reasonable

length of time before it has to be withdrawn and replaced by fresh solution.

Peritoneal dialysis is not intended to be a drug delivery system. However, it has at times been used as such; when the patient suffers from diabetes, as well as renal failure, insulin may be added to the dialysis solution; part or all ofthe patient's insulin requirement is in this way administered not intravenously, as is usual, but from the peritoneum.

The possibility of using a peritoneal dialysis solution solely for parenteral drug delivery has not been attractive in the past, because the side-effects of peritoneal dialysis can be quite severe. Conventional peritoneal dialysis solutions, which use dextrose as an osmotic agent, are strongly hypertonic to the blood plasma and therefore exert such stress on the peritoneal membrane as to risk damage to that mebrane. This hypertonicity also appears to destroy peritoneal macrophages, thereby compromising the host defence system for preventing infection, and thus increasing the likeliehood of peritonitis. Also, peritoneal dialysis with glucose solutions causes the patient to receive a massive influx of glucose, which can cause obesity and other problems. These potentially serious complications resulting from peritoneal dialysis are tolerable when the patient is suffering from renal failure, for which treatment is imperative if the patient is to survive, but are not lightly to be risked in the case of a patient whose illness does not involve loss of renal function and who therefore does not need dialysis.

The solutions used in the present invention do not rely on dextrose as an osmotic agent. Instead they contain a mixture of glucose polymers. The use of glucose polymers as osmotic agents in peritoneal dialysis has been described in British specifications Nos. 2132914 A and 2154469 A. With the aid of such polymers it is possible to formulate a solution which is substantially isotonic to the patient's blood, thereby minimising any danger of damaging the peritoneal membrane or impairing the host defence system; also, since the solution need contain little or no glucose the problems associated with giving the patient too much glucose are avoided.

The method of the invention may be used for intraperitoneal administration of many drugs for which enteral administration is unsatisfactory but is especially useful for delivery of peptide drugs, and will be described with reference to such drugs. Examples of such drugs are erythropoetin and growth hormone.

The solutions of the invention may contain, in addition to the glucose polymer mixture and the peptide drug, electrolytes corresponding to those present in human blood. Ideally, the concentrations of these electrolytes in the solutions are the same as in the blood, so as to minimise the extent to which the presence of the solution in the peritoneal cavity causes the composition of the blood to be changed due to diffusion of electrolytes across the peritoneal membrane. The range of concentrations and the nature of such electrolytes are similar to those in the solutions used in peritoneal dialysis. Suitable concentration ranges for most purposes are, for example, as follows:-

Na	115 - 140	mmol/l
Cl	95 - 145	mmol/l
Mg	0.6 - 0.9	mmol/l
Ca	1.0 - 5.0	mmol/l
Lactate	30 - 40	mmol/l

When formulating peritoneal dialysis solutions for treatment of renal failure, it is essential that the composition is such as to be capable of causing sustained ultrafiltration, i.e. a net transfer of water from the blood through the peritoneal membrane into the peritoneal cavity. By contrast, the solutions of the

invention, used for peptide drug delivery, are not normally intended to produce sustained ultrafiltration.

The purpose of the invention is to provide in the peritoneal cavity a depot of the peptide drug, from which the drug is slowly released into the blood of the patient. As mentioned above, the molecules of peptide drugs are too large and electrically charged to pass easily through the gut wall; these characteristics also render the molecules incapable of readily passing through the peritoneal membrane. Escape of the peptide drug molecules from the peritoneal cavity appears to be mainly by way of passage of the molecules into the lymphatic system. This takes place at only a slow rate and results in a steady trickle of the drug into the blood, which then delivers the drug to its site of action. In this way, the major difficulties of administering peptide drugs (poor absorption from the gut and limited duration of activity when in the blood) are avoided.

Since ultrafiltration is not normally needed, the solution can be formulated with a view to arriving as rapidly as possible at an equilibrium between the blood and the solution, such that the volume of liquid within the peritoneum remains substantially unchanged by the exchanges which continuously take place across the peritoneal membrane. This ideal objective is not attainable in practice but the characteristics of the glucose polymers contained in the solution make it feasible to achieve an approximate equilibrium in most respects. These polymers are of a relatively large molecular size so that, unlike dextrose, they do not easily pass through the peritoneal membrane. The

concentration of the glucose polymer mixture in the solution can be selected to cause only a limited amount of ultrafiltration. An ideal situation is one in which there is no gain or loss across the peritoneal membrane.

The solution is allowed to remain in the peritoneal cavity until such time as the concentration therein of the peptide drug has fallen to a level at which the rate of supply of the drug through the lymphatic system is no longer therapeutically effective (as indicated, for example, by sampling the blood to determine the peptide drug content thereof). The solution is then withdrawn from the peritoneal cavity and is replaced by fresh solution.

The glucose polymer mixtures used in the present invention are such as are described in British specification No. 2154469 A. They contain more than 50%, preferably from 90 to 100%, by weight of glucose polymers of D.P. greater than 12. The concentration of the glucose polymer mixture in the solution is chosen in accordance with the initial osmolality desired, and with a view to achieving as nearly as possible an equilibrium between the blood and the solution in the peritoneum. The weight average molecular weight is preferably from 15,000 to 25,000.

The concentration of the peptide drug in the solution may be varied in accordance with what is found by experiment to produce satisfactory therapeutic activity for the drug being administered.

As indicated, the solutions of the invention are not primarily intended for use in peritoneal dialysis. However, if

the patient happens to be suffering from renal failure as well as from the condition for which the peptide drug is being administered, the solution can be formulated to effect ultrafiltration as well as delivery of the peptide drug. In effect, the patient can be treated with a dialysis solution appropriate to provide the ultrafiltration needed to counteract the effects of renal failure, to which solution the peptide drug has been added; the concentrations of the components of the solution other than the peptide drug are modified as may be necessary in order to preserve the desired initial osmolality of the solution. Such a solution will contain a higher conentration of the glucose polymer mixture than is needed in a solution used simply for drug delivery. In general, the range of concentration of the glucose polymer mixture in the solutions of the invention can for most purposes be expected to be within a range of from 0.5 to 10% w/v.

The following Example is given by way of illustration of the invention.

EXAMPLE

A composition suitable for introduction into the peritoneal cavity of a patient to effect treatment of anaemia, caused by a deficiency of erythropoeitin, consists of an aqueous solution containing:-

Erythropoietin (microgram/litre)	10 - 100
Glucose polymer mixture (g/l)	10
Na (mmol/l)	132
Ca (mmol/l)	1.75

Mg (mmol/l)	0.75
Cl (mmol/l)	99
Lactate (mmol/l)	35

The glucose polymer mixture in this solution was the glucose polymer mixture desribed in Example 2 of British specification No. 2154469 A. It contains 91.9% of polymers of D.P. greater than 12 and 7.9% of polymers of from D.P. 2 to 10, and has a weight average molecular weight of 23,700.

Reference has been made above to compositions containing a peptide drug. However, it should be appreciated that the present invention has application with regard to drugs other than peptide drugs, particularly for those which cannot be given orally but can be given parenterally. Such drugs include many cephalosporin antibiotics.

CLAIMS

1. A pharmaceutical composition for intraperitoneal administration of a drug, comprising an aqueous solution containing said drug and a glucose polymer mixture which includes at least 50% by weight of glucose polymers of D.P. greater than 12.

2. The composition of Claim 1, wherein said drug cannot be taken orally.

3. The composition of Claim 1 or Claim 2, wherein said drug is a peptide drug.

4. The composition of Claim 1, wherein said peptide drug is erythropoeitin.

5. The composition of Claim 1 or Claim 2, wherein said drug is a cephalosporin antibiotic.

6. The composition of any of Claims 1 to 3, wherein said glucose polymer mixture has a weight average molecular weight of from 15,000 to 25,000.

7. The composition of any of Claims 1 to 4, wherein the solution contains:

Na	115-140 mmol/l
Cl	95-145 mmol/l
Mg	0.6-0.9 mmol/l
Ca	1.0-5.0 mmol/l
Lactate	30-40 mmol/l

8. The composition of any of Claims 1 to 7, wherein the solution contains from 0.5 to 10% w/v of said glucose polymer mixture.

9. The composition of any of Claims 1 to 7, wherein the osmolality of said solution is from 290 to 320 mOsm/kg.

10. A pharmaceutical composition substantially as hereinbefore described with reference to the example.

11. A method of administering a drug to a patient comprising introducing the peritoneal cavity of the patient a composition as claimed in any of Claims 1 to 10.

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